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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE		
	Application Number	09/807,458
	Filing Date	July 5, 2001
	First Named Inventor	Carmen Almansa
	Group Art Unit	1626
	Examiner Name	Kamal A. Saeed
	Attorney Docket Number	1604-129

Title of the Invention: **Novel Imidazoles with Anti-Inflammatory Activity**

DECLARATION UNDER 37 C.F.R.§1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Carmen Almansa, Ph.D., do solemnly declare that:

1. I am the same Carmen Almansa listed as the inventor on the above-referenced patent application.

2. I received a Ph.D. in Organic Chemistry from the University of Barcelona, Spain in 1989. I have been a Senior Medicinal Chemist at the R&D Center of J. Uriach & Cia since 1989.

3. I have read and understood the Office Action dated December 31, 2002, issued in connection with the present application.

4. In this Office Action, the Examiner rejects pending claims 1-13 and 23-29 under 35 U.S.C. §103(a) as obvious over International Patent Publication WO 96/03387 to Weier et al (hereinafter referred "Weier et al."). The Examiner asserts that the compounds taught by Weier et al. are isomers of Applicants' claimed compound wherein R_1 is methyl, R_2 is halogen substituted phenyl, R_3 is C1-8 alkyl, X is C and Y is N. The Examiner states that nothing unobvious is seen in substituting the claimed compounds for the structurally similar isomers taught by Weier et al., since such structurally related compounds suggest one another and would be expected to share common properties.

5. However, as will be discussed below, the compounds according to the present invention are unexpectedly more potent COX-2 inhibitors than the compounds of Weier et al.

6. We have performed *in vitro* tests to determine COX-2 activities of compounds within the scope of the claimed invention by obtaining their IC_{50} values against COX-2 in human cell lines, in particular in 143982 cells following the method disclosed in Almansa et al, *J. Med. Chem.* **2001**, *44*, 350-361. The results of these tests are reflected in Table A, which, on information and belief, accompanies this declaration. The left column of Table A lists the compounds tested, the right column lists our measurements of COX-2 inhibition in 143982 cells as IC50 values [μM]. The middle column identified the Example in the current application in which the respective

compound is discussed. The first row of Table A shows our measurement of the respective IC_{50} value for celecoxib. Celecoxib (Celebrex) is a COX-2 inhibitor which often serves as a reference compound in COX assays.

7. As demonstrated by the IC_{50} values listed in Table A, the compounds of the present invention are significantly more active than celecoxib. For example the compound of example 13(5) is shown to have an almost 16 times better activity than celecoxib (IC50 [μM] 0.005 vs. 0.079).

8. Weier et al. shows in the results of assays for COX-2 activity in Table 2 on pages 196 and 197, ID50 values [μM] for a number of the compounds disclosed by Weier et al. Table 2 of the patent does not disclose a ID50 for celecoxib. However, Weier et al. and his co-inventors published a paper, in which they discussed the activities of selected compounds disclosed in Weier et al. This paper, which is entitled "Anti-inflammatory 4,5-Diarylimidazoles as Selective Cyclooxygenase Inhibitors" (hereinafter "Barta et al.") is submitted with this declaration for the Examiner's review. The paper discloses the results of *in vitro* activity studies of selected compounds of Weier et al. as well as of celecoxib against human recombinant COX-2 enzyme. The activities reported in the Barta et al paper are in agreement with the activities reported for the same compounds in Weier et al.

9. From a review of Table 1 of Barta et al., it is apparent that all 4,5-Diarylimidazole compounds listed therein are less potent than celecoxib. Compound 4f which is discussed in the body of the paper displays an activity that is about one third of that of celecoxib, while compound 4m, which is the most potent compound disclosed, has a COX-2 activity that is slightly more than half of the activity of celecoxib.

10. It is my professional opinion that although the COX-2 assay in Barta et al and our assay are not identical, the values disclosed in Table A and the values disclosed in Barta et al. are fully comparable as they can both be put into relation to the disclosed IC_{50} of a reference compound, celecoxib.

11. From an indirect comparison of the IC_{50} of 1-(4-Fluorophenyl)-2-methyl-5-(4-methylsulfonylphenyl)imidazole (Example 6 of the present application), which is the claimed compound, wherein R_1 is methyl, R_2 is 4-fluorophenyl, R_3 is CH_3, X is C and Y is N and which is one of the compounds that the Examiner alleges to be obvious over Weier et al. and the IC_{50} of 5-(4-Fluorophenyl)-2-methyl-4-(4-methylsufonylphenyl)-1H-imidazole (Example 6 of Weier et al.) shown in Weier et al.'s Table 2 on pages 196-197, it could be determined that 1-(4-Fluorophenyl)-2-methyl-5-(4-methylsulfonylphenyl) imidazole is about 90 times more active than 5-(4-Fluorophenyl)-2-methyl-4-(4-methylsufonylphenyl)-1H-imidazole.

12. It is my professional opinion that the activities of the compounds claimed in the present invention and measured in our laboratory as shown in Table A, are directly comparable to the activities measured by and shown in the Barta et al. paper, which describes the activities of selected compounds disclosed in Weier et al., and indirectly to compounds listed in Table 2 of Weier et al.

13. It is also my professional opinion that a comparison of the activities shown in Table A and Table 1 of the Barta et al. reference demonstrate that the compounds according to the presently claimed invention have activity levels that are significantly superior to the activities reported in Weier et al.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

27-6-03
Date

Carmen Almansa, Ph.D.
Inventor

1604-129-declaration

Tabl A

Compound Name	Example No.	COX-2 inhibition in 143982 cells (IC50 value, μM)
Celecoxib (reference product)	--------	0.079
4-Chloro-5-(4-fluorophenyl)-1-(4-methylsulfonylphenyl)imidazole	4	0.014
4-Chloro-5-(4-methylphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(1)	0.016
4-Chloro-5-(2,4-difluorophenyl)-1-(4-methylsulfonylphenyl)imidazole	4(2)	0.007
4-Chloro-5-(3,4-dichlorophenyl)-1-(4-methylsulfonylphenyl)imidazole	4(4)	0.006
4-Chloro-5-(4-methoxyphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(5)	0.011
4-Chloro-5-(3-fluoro-4-methoxyphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(6)	0.004
4-Chloro-5-(3-fluorophenyl)-1-(4-methylsulfonylphenyl)imidazole	4(7)	0.065
4-Chloro-5-(3-fluoro-4-methylphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(8)	0.006
4-Chloro-5-(2-fluorophenyl)-1-(4-methylsulfonylphenyl)imidazole	4(9)	0.028
4-Chloro-5-(2-fluoro-4-methoxyphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(12)	0.015
4-Chloro-5-(3-methoxy-4-methylphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(14)	0.015
4-Chloro-5-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)imidazole	4(15)	0.018
4-Chloro-5-(4-ethoxyphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(22)	0.004
4-Chloro-5-(4-methylsulfanylphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(24)	0.011
4-Chloro-5-(4-ethylsulfanylphenyl)-1-(4-methylsulfonylphenyl)imidazole	4(25)	0.053
4-Bromo-5-(4-fluorophenyl)-1-(4-methylsulfonylphenyl)imidazole	5	0.036
1-(4-Fluorophenyl)-2-methyl-5-(4-methylsulfonylphenyl)imidazole	6	0.051
2-Chloro-1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)imidazole	7	0.014
2-Bromo-1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)imidazole	9	0.048
1-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)imidazol-2-carbonitrile	10	0.051

4-[4-Chloro-5-(4-fluorophenyl)imidazol-1-yl]benzenesulfonamide	13	0.018
4-(4-Chloro-5-phenylimidazol-1-yl)benzenesulfonamide	13(1)	0.009
4-[4-Chloro-5-(3,4-dichlorophenyl)imidazol-1-yl]benzenesulfonamide	13(2)	0.002
4-[4-Chloro-5-(4-methylphenyl)imidazol-1-yl]benzenesulfonamide	13(3)	0.003
4-[4-Chloro-5-(4-ethoxyphenyl)imidazol-1-yl]benzenesulfonamide	13(4)	0.002
4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)imidazol-1-yl]-benzenesulfonamide	13(5)	0.005
4-Chloro-5-(3-chloro-4-dimethylaminophenyl)-1-(4-methyl-sulfonylphenyl)imidazole	17c	0.027
4-Chloro-5-(4-methoxy-3-methylphenyl)-1-(4-methylsulfonylphenyl)imidazole	-------	0.013
4-Chloro-5-(4-chloro-3-methylphenyl)-1-(4-methylsulfonylphenyl)imidazole	-------	0.011

Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 3443–3448

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

ANTIINFLAMMATORY 4,5-DIARYLIMIDAZOLES AS SELECTIVE CYCLOOXYGENASE INHIBITORS

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Received 2 July 1998; accepted 12 October 1998

Abstract: The synthesis and activity of a series of 4,5-diarylimidazole analogs are described. One analog had an IC_{50} of 80 nM, was 6750-selective against COX-1, and demonstrated in vivo potency in the mouse air pouch model. © 1998 Elsevier Science Ltd. All rights reserved.

Chemistry

It has been recently discovered that the body contains at least two isoforms of cyclooxygenase: COX-1 and COX-2.[1] COX-1 is thought to be involved in normal metabolic housekeeping, for example, cytoprotection of the stomach lining. COX-2 is present in inflamed tissues. Unselective cyclooxygenase inhibitors which disrupt the action of COX-1, such as aspirin and ibuprofen, can lead to stomach ulcers. This effect can be dose limiting in patients with chronic inflammatory conditions, such as osteoarthritis. Clinical studies support the hypothesis that the newer, COX-2 selective inhibitors show an improved safety profile vs. traditional non-steroidal antiinflammatory drugs.[1]

We embarked on a discovery project to identify COX-2 selective 4,5-diarylimidazoles. 4,5-Diarylimidazoles had been proposed as possible antiinflammatory agents previously,[2] and, thus, seemed like a logical starting point for our research. Studies suggested that COX-2 selectivity could be easily conferred by incorporation of a suitably disposed methyl sulfone or sulfonamide pharmacophore.

Our first imidazole synthesis (Scheme 1) adopted a general synthetic approach similar to one described by Lombardino,[2] proceeding from a benzoin condensation.[3] The benzoin condensations were facilitated by converting either of the aldehyde components into *O*-trimethylsilyl cyanohydrins. Oxidation of the resulting benzoins 1 to benzils 2a using either copper sulfate in pyridine conditions or Rigby's method involving bismuth (III) oxide in acetic acid[4] proved successful, but unsatisfactory due to difficulty in product isolation and generally poor yields. In contrast, the Swern oxidation[5] proved reliable and effective. The benzils thus obtained were condensed with ammonium acetate/triflouroacetaldehyde ethyl hemiacetal. *S*-methyl substituted intermediates 3 were easily oxidized to the crystalline sulfones 4 with hydrogen peroxide in acetic acid. This route addressed early compound needs, but presented a few difficulties. The benzoin condensation step was capricious and difficult to scale, and toxic HCN was produced in the hydrolysis. With these limitations in mind we developed a shorter, more modern sequence, eliminating the condensation step and employing Wittig methodology to form the key carbon–carbon bonds (Scheme 2). Benzylic phosphonium salts 5, often available off-the-shelf, were deprotonated to make the corresponding ylids and condensed with 4-(mercaptomethyl)benzaldehyde.

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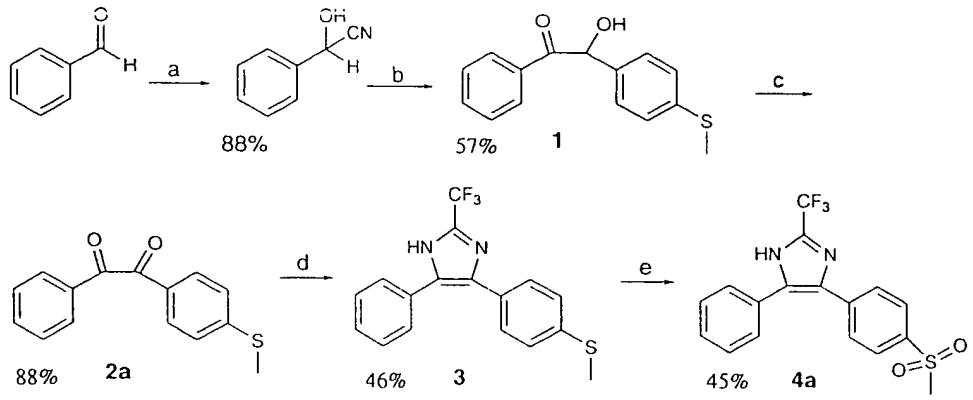
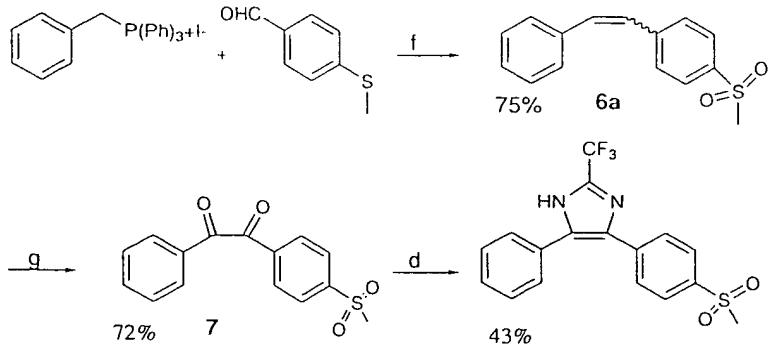
PII: S0960-894X(98)00627-1



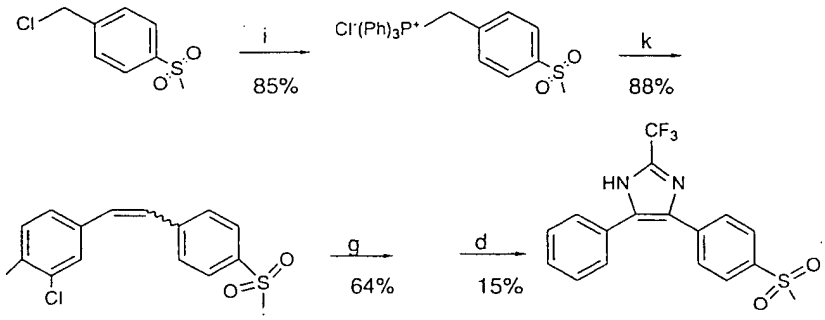
Scheme 1. *Reagents and Conditions*: (a) TMS-CN, ZnI_2; (b) LiHMDS/THF/-78 °C, then 4-(MeS)-benzaldehyde, then hydrolysis; (c) DMSO/TFA_2O/CH_2Cl_2/-55 °C; (d) NH_4OAc/$CF_3CH(OEt)(OH)$/AcOH/reflux; (e) H_2O_2/AcOH/100 °C.

The resulting stilbenes **6**, which were *cis–trans* mixtures, were chemoselectively oxidized to sulfones[6] using Oxone™. It was necessary at this point to expediently transform the stilbenes into benzils **7a**. This was cleanly and easily accomplished using $KMnO_4$ in acetic anhydride.[7] These conditions converted both double bond isomers, and we did not observe C–C bond cleavage, a known complication of some metal mediated oxidations of α heteroatom substituted carbonyl compounds. The benzils obtained could be carried forward as in Scheme 1.



Scheme 2. *Reagents and Conditions*: (f) LiOEt/EtOH/ambient, then Oxone™/MeOH (aq) /0 °C to ambient; (g) $KMnO_4$/Ac_2O/0 °C; (d) NH_4OAc/$CF_3CH(OEt)(OH)$/AcOH/reflux.

In Scheme 3, 4-(methanesulfonyl)-benzyl chloride[8] was used to further streamline the sequence. In this case, the ylid was somewhat less reactive due the electron-withdrawing sulfone, so heating was required to effect stilbene formation. The stilbene was oxidized to the benzil and carried on as in the previous schemes.



Scheme 3. *Reagents and Conditions*: (i) triphenylphosphine/toluene/reflux; (k) aldehyde/LiOEt/EtOH/reflux; (g) $KMnO_4/Ac_2O/0$ °C; (d) NH_4OAc /$CF_3CH(OEt)(OH)$/AcOH/reflux.

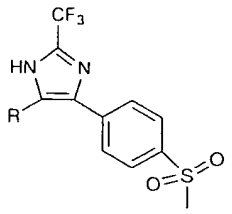
Discussion

Table 1 shows the biological data for in vitro COX-2 and COX-1 enzyme inhibition, and the results of in vivo testing in the mouse air-pouch assay.[9] It is clear that some very potent analogs that exhibit significant selectivity were identified, notably the analogs with mid-sized substituents (e.g., chloro) in the 3-position of the aryl group. Analog **4f**, for example, shows 6750-fold selectivity and good activity in the air pouch (98% inhibition @ 2 MPK). These results differ somewhat from the known art exemplified by compounds such as Celecoxib, where 4-substitution was preferred,[10] but as with that series, subtle changes on the aryl rings, such as changing from H- to F- may have significant impact on the in vitro activity.

Experiences with Celecoxib and other diarylheterocycles showed that, although sulfonamides typically have poorer in vitro COX-2/COX-1 selectivity than the corresponding sulfones; sulfonamides sometimes have superior in vivo potency.[10] We wished to assess whether sulfonamides offered any advantages in the present case. Several analogs were transformed from sulfones into sulfonamides. The imidazole N-H was protected using SEM-Cl/NaH/THF. Using Huang's[11] methodology, the methyl of the methylsulfone was cleaved with triethylborane, and the resulting sulfinate anion was reacted with hydroxylamine-*O*-sulfonic acid. The SEM protecting group was subsequently removed with fluoride. One of the analogs prepared in this manner, 5a, was only 110-fold selective and actually showed poorer in vivo activity. Since the results for sulfonamides were not encouraging, we renewed our focus on the sulfones.

Other modifications we tried in the sulfone series included methylation of of the imidazole N-H and replacement of the imidazole-(2)-trifluoromethyl moiety with various alkyl, aryl, and alkenyl groups, including furyl and isopropyl.[9] Some trifluoromethyl substitutions demonstrated good enzyme activity, but all 2-variants tested showed significantly reduced in vivo efficacy. It is not required for the substituent R- to be phenyl; compound 4s in Table 1 exemplifies an analog with enzyme and in vivo activity where R- is a heterocycle.

Table 1

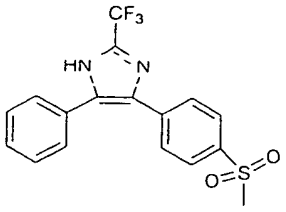


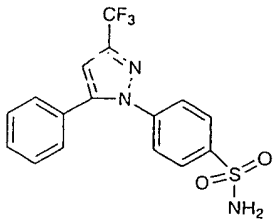
	R	H-COX-2[a] (μ Mol)	H-COX-1 (μ Mol)	Air Pouch[b] (% inh.@ 2 MPK)
4a	phenyl	0.69	1580	95
4b	2-F-phenyl	3.0	>100	
4c	3-F-phenyl	0.24	>100	92
4d	4-F-phenyl	0.19	>100	99
5a	4-F-phenyl (sulfonamide)	0.10	11	33
4e	2-Cl-phenyl	1.3	>100	86
4f	3-Cl-phenyl	0.080	540	98
4g	4-Cl-phenyl	0.37	10	86
4h	2-Me-phenyl	1.8	>100	
4i	3-Me-phenyl	0.61	>100	29
5b	3-Me-phenyl (sulfonamide)	0.15	6.2	
4j	4-Me-phenyl	0.65	33	
4k	3-MeO-phenyl	2.4	>100	
4l	4-MeO-phenyl	2.9	5.6	
4m	3,4-di-Cl-phenyl	0.04	10	84
4n	2,4-di-F-phenyl	0.55	>1000	100
4o	3,4-di-F-phenyl	0.16	760	68
4p	3-Cl-4-Me-phenyl	0.23	56	0
4q	3-F-2-Me-phenyl	1.7	1000	94
4r	cyclohexyl	4.0	>100	
4s	2-thienyl	1.4	>1000	79
4t	3-thienyl	2.0	>100	0
4u	3-pyridyl	2.4	>100	29

[a]Human recombinant COX enzymes. [b]Mouse air pouch assay

In conclusion, potent diarylimidazole sulfones which compare pretty favorably with Celecoxib were synthesized, with 4f showing the best profile overall. A typical inhibitor, **4a**, was carried forward through the rat adjuvant arthritis model. It is somewhat less active than Celecoxib in vitro (690 vs. 28 nM), but shows excellent activity in efficacy models.

Table 2





	4a	Celecoxib
COX-2 (μMol)	0.69	0.028
COX-1 (μMol)	1600	15
Air Pouch ED_{50} (MPK)	0.38	0.33
Adj. Arth. ED_{50} (MPK)	0.16	0.37

Representative Procedure for Synthesis of Stilbene Sulfones (6a)

Benzyl triphenylphosphonium iodide (9.61 g, 20 mMol) was suspended in abs EtOH and cooled to 0%C. *n*-BuLi (13.1 mL, 21 mMol) was added dropwise. 4-(Methylmercapto)-benzaldehyde (2.67 mL, 20 mMol) was added and the mixture was allowed to stir for 2.5 h at rt, then diluted with water (40 mL) and extracted with methylene chloride (200 mL). The organic layer was dried using $MgSO_4$, filtered through a silica plug (which removed most of the triphenylphosphine oxide), and concentrated to a yellow semi-solid. The solid was diluted with MeOH (50 mL), cooled to 0%C, and treated with Oxone™ (50 mMol) in water (100 mL). After 15 min, the cooling bath was removed and the mixture was stirred at rt for 1.5 h. The suspension was extracted with methylene chloride (200 mL, then 2 × 50 mL). The combined organic layers were dried over $MgSO_4$ filtered through silica, concentrated , and chromatographed (2/1, hexane/ethyl acetate) to afford the desired **6a** (3.95 g, 75%) as a mixture of *cis–trans* isomers.[12]

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